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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/734,847	12/12/2000	C. Frank Bennett	ISIS0170-100(ISPH-0524)	4732

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 02/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/734,847	BENNETT ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-49,51 and 53-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-49,51 and 53-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9-1-05; 12-1-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

2. Applicant's arguments with regards to the grounds of rejection set forth in the prior Office Action are moot in view of the new grounds of rejection set forth below.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 34-49, 51, and 53-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moulds et al. in view of Cantin et al. (US Patent No. 5,110,802) and Manoharan et al. (US Patent No. 6,043,352).

Moulds et al. teach the design of antisense oligonucleotides having such high affinity for RNA that they form a nearly irreversible complex, thereby inactivating the RNA via a non-RNAse H, or steric block mechanism (p. 5045, para. 2). Moulds et al. disclose modified antisense oligonucleotides comprising phosphorothioate, 2'-O-allly, and C-5 propyne modifications. Moulds et al. teach a splicing assay using C-5 propyne, phosphorothioate-modified oligonucleotides targeting the 5'-splice site of TAg RNA. The presence of this oligonucleotide complexed to Tag RNA resulted in 100% inhibition of splicing and blocked translation of the RNA (see table 4, page 5051). The

oligonucleotides of Moulds et al. are designed to target 5'-splice junctions, and polyadenylation signals, see for example Table 1.

Moulds et al. do not teach wherein their disclosed antisense oligonucleotides comprise a 2'aminooxy modification or 3'-methylphosphonate internucleoside linkages. Additionally, Moulds et al. do not teach wherein substantially every sugar comprises a 2'-aminooxy modification, or wherein the modulation of splicing comprises a reduction in the frequency of the use of a 5'splice site, a redirection of splicing, an altered ratio of splice products, or results in the exclusion of one or more exons from a mature mRNA. Moreover, Moulds et al. does not teach that the wild-type cellular mRNA target is an mRNA encoding a receptor.

Cantin et al. disclose antisense oligonucleotides comprising oligoribonucleoside methylphosphonates (OMP), wherein a 3'-5' methylphosphonate linkage replace the phosphodiesters linkage found in naturally occurring nucleic acids. The 8 base OMP is complementary to the first splice acceptor site of the tat III gene. The OMP attacks the splice acceptor site to block the splicing of the RNA product of the tat III gene (See col. 2).

Manoharan et al. teach 2'-O-[2-(2-N,N-dimethylaminoethyl)oxyethyl]-5-methyl modified oligonucleotides to reduce the levels of ICAM-1 (a cellular protein with potential function as a receptor) in treated HUVEC cells. The oligonucleotides are believed to work by a direct binding RNase H independent mechanism. (See bridging paragraph of col. 14-15). Additionally, Manoharan et al. teach the design of antisense

compounds comprising wherein each sugar comprises a 2'-aminooxy modification (see Table 1, col. 15.).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the teachings of Moulds et al. with the teachings of Cantin et al. and Manoharan et al. in the design of the instant invention. One of ordinary skill in the art would have been motivated to substitute the 2'-O-ally modifications in their disclosed antisense oligonucleotides with the 2'-aminooxy modifications taught by Manoharan et al., because the 2'-aminooxy modifications of Manoharan et al. are disclosed to function by a non-RNAse H mechanism in the same manner as the modified antisense oligonucleotides of Moulds et al. Moreover, according to MPEP § 2144.06, it is *prima facie* obvious for the ordinary skilled artisan to substitute equivalents known for the same purpose. In the instant case, it would have been obvious to substitute the modified oligonucleotides of Moulds et al. with the functionally equivalent (i.e. having the ability to inhibit the expression of a target mRNA via a non-RNAse H mechanism) 2'-aminooxy modified antisense oligonucleotides of Manoharan et al. Additionally, the prior art teaches that oligonucleotides comprising 3'methylphosphonate internucleoside linkages can be used to design antisense compounds which function to block the splicing of an RNA target, it would have been obvious to modify the antisense compounds of Moulds et al. with the teachings of Cantin et al. with the expectation that the antisense compounds produced from this combination would also function to modulate splicing of any mRNA target comprising splicing associated domains, according to the present invention.

Although Moulds et al. do not teach that by designing antisense compounds to target intron/exon junctions, splicing will be modulated by producing an altered ratio of splice products, redirection of splicing, or resulting in the exclusion of one more exons, one of skill in the art would have recognized that these results are all potential consequences of disrupting the normal splicing machinery in a cell by antisense blockage of the intron/exon junctions within a wild-type mRNA target. Moreover, absent evidence to the contrary, the methods of modulating the processing of an mRNA target as taught by the combination of the instant references would be applicable to any wild-type cellular mRNA target as long as the target comprises the regions associated with regulating the processing of the target, for example those taught by Moulds et al. in Table 1, page 5045.

Conclusion

5. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 12/01/05 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 9:30 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 517-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Janet L. Epps-Ford
Primary Examiner
Art Unit 1633

JLE